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09/896,186	06/29/2001	Joshua Levin	PB/5-31481A	9567

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EXAMINER	
MEHTA, ASHWIN D	
ART UNIT	**PAPER NUMBER**
1638	13

DATE MAILED: 01/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No.	Applicant(s)	
	09/896,186	LEVIN ET AL.	
	Examin r	Art Unit	
	Ashwin Mehta	1638	

-- The MAILING DATE of this c mmunication appears n the cover sheet with th correspondence address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-59* is/are pending in the application.

4a) Of the above claim(s) *1-24,30-37,40-42,48-50 and 55-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-29,38,39,43-47,51-54,58 and 59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5,12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply* .

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group IV, claims 25-30, 39, 40, 44-48, 52-55, 59, and 60, and SEQ ID NO: 23 in Paper No. 11, received 29 October 2002 is acknowledged. S

NOTE: The original claims are missing a claim numbered 28. In accordance with 37 CFR 1.126, claims 29-60 have been renumbered 28-59, respectively. Claims 25-29, 38, 39, 43-47, 51-54, 58, and 59 have been examined in this Office action.

Subject matter in the claims that are drawn to non-elected inventions should be removed.

Information Disclosure Statement

2. The entry for Hartung et al., document "AF," in the IDS received 04 November 2002 was lined through only because the entry already appears, and was initialed by the Examiner, in the IDS received 24 August 2001.

Specification

3. The substitute specification filed 20 July 2001 has not been entered because it does not conform to 37 CFR 1.125(b) because the statement as to a lack of new matter under 37 CFR 1.125(b) is missing. However, the substitute specification introduces new matter (new sequences). If the substitute specification were entered, then the specification would be objected to for containing new matter, and Applicants would be required to remove it. Preliminary amendments do not enjoy original disclosure status. See MPEP 608.04(b).

Sequence Listing

4. The computer-readable form (CRF) of original sequence listing was found to have errors. Applicants are required to submit a new CFR, which does not contain the new matter present in the substitute specification. See the accompanying Notice to Comply.

Claim Objections

5. Claims 58 and 59 are objected to because of the following informalities: In line 1 of both claims, the article "A" should be --The--. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. Claims 25-29, 38, 39, 58, and 59 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claims are broadly drawn towards any plant cell comprising any endogenous nucleotide sequence identical or substantially similar to SEQ ID NO: 23, wherein said plant cell comprises a mutation in said endogenous nucleotide sequence or in any regulatory region thereof; or wherein the mutation is due to insertion of any nucleic acid molecule; a plant comprising said plant cell, or seed or progeny thereof; or wherein the mutation is a deletion, rearrangement, or point mutation.

The plant cells, plants, and seed and progeny thereof, as claimed, have the same characteristics as those found naturally and therefore do not constitute patentable subject matter. See American Wood v. Fiber Disintegrating Co., 90 U.S. 566 (1974), American Fruit Growers v. Brodgex Co., 283 U.S. 2 (1931), Funk Brothers Seed Co. v. Kalo Inoculant Co., 33 U.S. 127 (1948), Diamond v. Chakrabarty, 206 USPQ 193 (1980). It is suggested that the claims be amended by inserting language that identifies products that cannot be found in nature.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 25-29, 38, 39, 43-47, 51-54, 58, and 59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 25, 43-47, 51-53: the recitation "substantially similar" renders the claims indefinite. It is not clear what nucleotide and amino acid sequences are and are not considered to be substantially similar to SEQ ID NOs: 23 and 24. The specification at pages 19-21 discusses the recitation. However, the specification does not define all of the nucleotide sequences that can be encompassed by the recitation. The specification indicates that a substantially similar nucleotide sequence is a nucleotide sequence that encodes a polypeptide that has substantially the same structure and function as the polypeptide encoded by the reference nucleotide sequence (paragraph bridging pages 19-20 and 20-21). However, it is not clear what is meant by

"substantially." The term does not indicate how different the structure and function can be. The specification also indicates that an example of such a substantially similar nucleotide or polypeptide sequence is one in which the encoded polypeptide only has changes not affecting the polypeptide function (paragraph bridging pages 19-20 and 20-21). However, this does not define all of the other nucleotide or polypeptide sequences that may also be considered substantially similar. The metes and bounds of the claim are not clear.

In claim 27: the claim recites the limitation "the insertion of a nucleic acid molecule comprises one T-DNA border region" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim or parent claim 25.

In claim 28: the claim recites the limitation "the insertion comprises a transposable element" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim or parent claim 25.

In claims 38 and 39: the claims are indefinite because it is not clear if the progeny and seeds also comprise the plant cell of claim 25.

In claim 43: the claim is indefinite because it does not recite any positive method steps. The claim indicates that the method comprises the step of altering the transcription or translation of the endogenous nucleotide sequence. However, anything that is done would obviously affect the transcription or translation of the endogenous nucleotide sequence.

In claims 44, 47, and 53: the recitation "chromosomal copy of the nucleotide sequence identical to...SEQ ID NO: 23" renders the claims indefinite. SEQ ID NO: 23 is a cDNA, and therefore is not present in chromosomes.

In claim 45: the recitation "a means" in line 4 renders the claim indefinite. It is not clear what is meant by the recitation.

In claim 46: the claim is indefinite because it is not clear how the expression of the nucleotide sequence is being altered. Regarding the nucleotide sequence, the claim only indicates that it is introduced into the cell. The expression level of the nucleotide sequence before the alteration is unknown. It is not clear how one is to define an alteration of expression when the level of expression before the "altering step" is unknown. How does one define the alteration in expression of the introduced nucleotide sequence versus a non-altered expression?

In claim 51: the recitations "stabilizing the expression in line 1 and "stabilized" in line 11 renders the claim indefinite. The recitations are indefinite because it is not clear if the method is for the expression of nucleotide sequences whose expression does not need to be stabilized. It is not clear what is considered stable versus unstable expression.

Further in claim 51: the recitation "in a plant cell of an endogenous nucleotide sequence of said plant cell or plant that encodes a polypeptide" in lines 3-4 renders the claim indefinite. Endogenous nucleotide sequences do not comprise plant cells. Further, while plant cells and plants may comprise a polypeptide, they are not referred to in the art as encoding a polypeptide.

Further in claim 51: the claim recites the limitation "said first expression cassette" in the last line. There is insufficient antecedent basis for this limitation in the claim.

In claim 54: the recitation "in a plant cell" in line 1 renders the claim indefinite. It is not clear if the plant cell in the recitation is the same plant cell mention in the claims from which claim 54 depends. It is suggested that the recitation be deleted.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 25-29, 38, 39, 43-47, 51-54, 58, and 59 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn towards any plant cell comprising any endogenous nucleotide sequence identical or substantially similar to SEQ ID NO: 23, wherein said plant cell comprises a mutation in said endogenous nucleotide sequence or in any regulatory region thereof; or wherein the mutation is due to insertion of any nucleic acid molecule; a plant comprising said plant cell, or seed or progeny thereof; or wherein the mutation is a deletion, rearrangement, or point mutation; a method for reducing the expression in a plant cell or plant of any endogenous nucleotide sequence identical or substantially similar to SEQ ID NO: 23 comprising modifying at least one chromosomal copy of said nucleotide sequence or regulatory region thereof by homologous recombination or by introducing into said plant cell a chimeric oligonucleotide that is capable of modifying at least one chromosomal copy of said nucleotide sequence or regulatory sequence thereof; a method for altering or stabilizing the expression of a nucleotide sequence of interest in a plant comprising reducing the expression in a plant cell or plant of any endogenous nucleotide sequence identical or substantially similar to SEQ ID NO: 23 comprising modifying at least one chromosomal copy of said nucleotide sequence or regulatory region thereof by homologous recombination or by introducing into said plant cell a chimeric

oligonucleotide that is capable of modifying at least one chromosomal copy of said nucleotide sequence or regulatory sequence thereof.

The specification describes a cDNA sequence (SEQ ID NO: 23) of an *Arabidopsis thaliana* protein that comprises an RNase D related domain. SEQ ID NO: 23 encodes the amino acid sequence set forth in SEQ ID NO: 24. The specification indicates that SEQ ID NO: 23 shares a high degree of similarity with an *A. thaliana* mRNA for an exonuclease named "wrnexo" in GenBank accession AJ404476, and that SEQ ID NO: 23 contains 9 extra bases that are not present in sequence encoding wrnexo (page 52, Example 7). The specification indicates that 3'-5' exonuclease domains comprise three subdomains designated as exo I, exo II, and exo III, and that these motifs are clustered around the active site and contain four negatively charged residues that serve as ligands for the two metal ions necessary for catalysis in addition to a catalytically active tyrosine. The specification indicates that 3'-5' exonuclease domains are found in DNA polymerases and the RNase D family of polypeptides, and that the domains are also referred to as RNase D related domains (page 22).

However, the specification does not describe any nucleotide sequences that are substantially similar to SEQ ID NO: 23 or regulatory region thereof, or any nucleotide sequences encoding polypeptides that are substantially similar to SEQ ID NO: 24. As discussed above, the specification indicates that numerous DNases and RNases can comprise 3'-5' exonuclease domains. However, not all of these proteins would share all of their functions with SEQ ID NO: 24. Zuo et al. for example (Nucl. Acids. Res., 2001, Vol. 29, pages 1017-1026), teach the members of the PDX protein family also have 3'-5' exonuclease activity (pages 1022-1023). However, this activity is not the same as all other proteins with 3'-5' exonuclease domains. The

specification does not describe the full functional activity of SEQ ID NO: 24, other than to indicate that it has a 3'-5' RNase domain. The specification does not correlate any of the other sequences of SEQ ID NO: 24 with its functional activity. As the specification does not completely describe the functional activity of SEQ ID NO: 24, one cannot correlate any sequences that differ from SEQ ID NO: 24 with its function. The specification does not describe how the sequence of SEQ ID NO: 24 can be changed without affecting its functional activity. As numerous different DNases and RNases comprise a 3'-5' exonuclease domain, the presence of this domain alone does not indicate that the protein shares the same functional activities as SEQ ID NO: 24. Further, the specification does not describe a single regulatory region of any endogenous nucleotide sequence, and the sequence of SEQ ID NO: 23 does not provide any information regarding any regulatory region of any endogenous nucleotide sequence. The specification also does not describe any mutation of any endogenous nucleotide sequences that are identical to or substantially similar to SEQ ID NO: 23, or any regulatory region thereof. The specification includes a discussion on methods for mutagenesis (pages 29-31). However, see Fiers 25 USPQ 2d (CAFC 1993) at 1606, which states that "[a]n adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself". Given the breadth of the claims encompassing endogenous nucleotide sequences that are substantially similar to SEQ ID NO: 23 or that encode SEQ ID NO: 24, and regulatory regions thereof, and any type of mutation of endogenous nucleotide sequences that are identical or substantially similar to SEQ ID NO: 23 or any regulatory region thereof, and lack of guidance as discussed

above, the specification fails to provide an adequate written description of the multitude of nucleotide sequences encompassed by the claims.

9. Claims 25-29, 38, 39, 43-47, 51-54, 58, and 59 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are broadly drawn towards any plant cell comprising any endogenous nucleotide sequence identical or substantially similar to SEQ ID NO: 23, wherein said plant cell comprises a mutation in said endogenous nucleotide sequence or in any regulatory region thereof; or wherein the mutation is due to insertion of any nucleic acid molecule; a plant comprising said plant cell, or seed or progeny thereof; or wherein the mutation is a deletion, rearrangement, or point mutation; a method for reducing the expression in a plant cell or plant of any endogenous nucleotide sequence identical or substantially similar to SEQ ID NO: 23 comprising modifying at least one chromosomal copy of said nucleotide sequence or regulatory region thereof by homologous recombination or by introducing into said plant cell a chimeric oligonucleotide that is capable of modifying at least one chromosomal copy of said nucleotide sequence or regulatory sequence thereof; a method for altering or stabilizing the expression of a nucleotide sequence of interest in a plant comprising reducing the expression in a plant cell or plant of any endogenous nucleotide sequence identical or substantially similar to SEQ ID NO: 23 comprising modifying at least one chromosomal copy of said nucleotide sequence or regulatory region thereof by homologous recombination or by introducing into said plant cell a chimeric

oligonucleotide that is capable of modifying at least one chromosomal copy of said nucleotide sequence or regulatory sequence thereof.

As discussed above, the specification describes a cDNA sequence (SEQ ID NO: 23) that encodes an *A. thaliana* protein that comprises an RNase D related domain (SEQ ID NO: 24). The specification indicates that SEQ ID NO: 23 shares a high degree of similarity with an *A. thaliana* mRNA for an exonuclease named "wrnexo" in GenBank accession AJ404476, and that SEQ ID NO: 23 contains 9 extra bases that are not present in sequence encoding wrnexo (page 52, Example 7). The specification indicates that 3'-5' exonuclease domains comprise three subdomains designated as exo I, exo II, and exo III, and that these motifs are clustered around the active site and contain four negatively charged residues that serve as ligands for the two metal ions necessary for catalysis in addition to a catalytically active tyrosine. The specification indicates that 3'-5' exonuclease domains are found in DNA polymerases and the RNase D family of polypeptides, and that the domains are also referred to as RNase D related domains (page 22).

However, the specification does not teach any nucleotide sequences that are substantially similar to SEQ ID NO: 23 or to nucleotide sequences that encode SEQ ID NO: 24 or regulatory sequences thereof. The specification does not provide any information that teaches how the sequences of SEQ ID NO: 23 or 24 can be changed without affecting their functional activity. As discussed above, numerous different DNases and RNases comprise a 3'-5' exonuclease domain, as exemplified by the discussion of different exoribonucleases of Zuo et al. The specification does not teach what the functions of SEQ ID NO: 24 are, other than that of having an RNase D related domain, or that all proteins having 3'-5' exonuclease domains can be used with the claimed methods. It is not clear how one skilled in the art can determine if the claimed

nucleotide sequences encode a polypeptide having the same function as SEQ ID NO: 24, when the full functional activity of SEQ ID NO: 24 is not described. The specification also does not teach a single mutant of SEQ ID NOs: 23 or 24 or their regulatory regions. Further, the mutated endogenous nucleotide sequences of the claimed plant cells encompass any type of mutation, including those that affect activities that do not affect the 3'-5' exonuclease activity, which are not taught. See In re Bell, 26 USPQ2d 1529, 1532 (Fed. Cir. 1993) and In re Deuel, 34 UPSQ2d, 1210 (Fed. Cir. 1995), which teach that the mere existence of a protein does not enable claims drawn to a nucleic acid encoding that protein. See also Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016 at 1021 and 1027, (Fed. Cir. 1991) at page 1021, where it is taught that a gene is not reduced to practice until the inventor can define it by "its physical or chemical properties" (e.g. a DNA sequence).

The specification also is not enabled for reducing the expression of SEQ ID NO: 24 by homologous recombination of SEQ ID NO: 23 or any regulatory region thereof. The specification only provides a general discussion about homologous recombination (page 29). No guidance is provided at all as to how one would use homologous recombination to reduce the expression of SEQ ID NO: 24. Homologous recombination has not been routinely reduced to practice in the art of plant molecular biology. Puchta (Plant Mol. Biol., 2002, Vol. 48, pages 173-182) discusses the state of gene replacement by homologous recombination in plants, and teaches that efficient gene targeting techniques in higher plants have not yet been achieved. Puchta teaches, for example, that improvements to gene targeting in animals have not been successful in plants (page 173), that extending the length of homology in the transferred DNA to up to 22 kb did not result in higher frequencies (page 174). Puchta discusses that results of gene

targeting in *Arabidopsis*, involving the AGL5 MADS-box gene (which is discussed in the references pointed out in the specification on page 29), have been controversial, and that no statistically sound conclusion as to the frequencies of targeting could be drawn from this single event (paragraph bridging pages 174-175). Terada et al. (Nature Biotech., 2002, Vol. 20, pages 1030-1034) also address the reports of gene targeting in *Arabidopsis*, and also assert that no one has yet repeated the experiments, and that the authors of one of those reports also detected the occurrence of undesirable events, including ectopic recombination and/or simultaneous ectopic integration of the transgene used (page 1030). While Terada et al. teach a method for homologous recombination in rice, it is noted that this method was not known at the time the instant invention was filed. Further, even if reproducible methods for homologous recombination were known in the art, the specification does not teach what sequences should be targeted. As numerous various DNases and RNases have 3'-5' exonuclease domains, if this region in SEQ ID NO: 23 was targeted, the method would also affect the genes encoding other, unrelated 3'-5' exonuclease domain-containing proteins. Undue experimentation would also be required to determine the target of the homologous recombination without also affecting other genes. As homologous recombination is required to practice the claimed method in all plant species, and that reproducible methods of homologous recombination were not known in the art for plant species other than Chlamydomonas at the time of the instant invention, undue experimentation would be required by one skilled in the art to practice the claimed method.

The specification also does not teach how one skilled in the art can use chimeric oligonucleotides to reduce the expression of the endogenous nucleotide sequences encoding SEQ ID NO: 24 or substantially similar sequences, or regulatory regions thereof. The specification

only contains several lines that very generally mentions chimeric oligonucleotides (paragraph bridging pages 29-30). The specification cites Zhu et al. (Proc. Natl. Acad. Sci., USA, 1999, Vol. 96, pages 8768-8773) as illustrating this technique. However, Zhu et al. only teach the used of RNA/DNA chimeric oligonucleotides in maize. Zhu et al. do not illustrate this technique in any other plant. Further, Zhu et al. knew in advance what sequences in their target gene to change, because the effect of changing those nucleotides was already known in the art (page 8770). The instant specification does even not provide any guidance concerning the nucleotides that one skilled in the art should change that would also not affect other genes encoding unrelated polypeptides, as discussed above. See Genentech, Inc. V. Novo Nordisk, A/S, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997), which teaches that "the specification, not the knowledge of one skilled in the art" must supply the enabling aspects of the invention. It is noted that SEQ ID NO: 23 is a cDNA, and therefore is not an endogenous nucleotide sequence in chromosomes.

Further, the specification does not teach what the effect on a plant would be in which the expression of the endogenous nucleotide sequence was reduced. The specification indicates that the nucleotide sequences of the invention are useful to manipulate or alter gene expression or post-transcriptional gene silencing (PTGS; page 27, 1st paragraph). However, the specification does not teach that any plants or plant cells in which the expression of SEQ ID NO: 23 is reduced were actually made. The basis for Applicants' conclusion that the nucleotide sequences of the invention affect gene silencing is therefore unknown. As plant cells with reduced expression of SEQ ID NO 24 have not been made, it is not clear what the overall effect of such a reduction on a plant cell or plant would be. Further, if SEQ ID NO: 24 is required for PTGS, then its inhibition would affect more than just the expression of a co-suppressed transgene.

Plants of course did not evolve gene silencing mechanisms just to silence transgenes. For example, plants use PTGS as a defense against viruses (for example, see Voinnet et al., PNAS, 1999, Vol. 96, pages 14147-14152). If PTGS is inhibited with the claimed invention, it is not clear what the overall effect on the plant would be, and it is not clear how one skilled in the art would use such a plant.

Further, the only manner in which the claimed method would alter the expression of the nucleotide sequence of interest is by increasing it, as expression of the endogenous nucleotide sequence of the claims is supposed to be reduced. If SEQ ID NO: 24 is essential to PTGS, then inhibition of PTGS by reducing the expression of SEQ ID NO 24 would only "lift" the co-suppression of any co-suppressed nucleotide sequence of interest that has been introduced into the plant cell. Further suppression could not be possible, since the PTGS mechanism is supposed to be inhibited. Furtherstill, the claimed methods would not effect the expression of introduced nucleotide sequences where the expression is inhibited due to transcriptional gene silencing. The instant specification itself teaches that the nucleotide sequences of the invention are supposed to affect PTGS (page 27, 1st paragraph). Furtherstill, it is not clear, in the absence of further guidance, how the claimed methods are to be used to increase or "stabilize" the expression of introduced nucleotide sequences of interest that have not been silenced. See Genentech, Inc. V. Novo Nordisk, A/S, *supra*. Given the breadth of the claims, unpredictability of the art and lack of guidance of the specification as discussed above, undue experimentation would be required by one skilled in the art to make and use the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 25, 29, and 59 rejected under 35 U.S.C. 102(b) as being anticipated by Elmayan et al. (Plant Cell, 1998, Vol. 10, pages 1747-1757) in light of Suzuki et al. (An Introduction to Genetic Analysis, 4th Edition, W.H. Freeman and Company, New York, 1989).

The claims are broadly drawn towards any plant cell comprising any endogenous nucleotide sequence identical or substantially similar to SEQ ID NO: 23, wherein said plant cell comprises any mutation in said endogenous nucleotide sequence or in any regulatory region thereof; or wherein expression of said endogenous nucleotide sequence is reduced; or wherein said mutation is a point mutation.

Elmayan et al. teach Arabidopsis plants mutagenized with EMS. The mutant plants showed decreased levels of PTGS. The mutated endogenous nucleotide sequence in the plant cells of Elmayan et al. is substantially similar to instant SEQ ID NO: 23. As discussed above, the instant specification does not clearly identify "substantially similar", and does not clearly define how different the function of a "substantially similar" nucleotide sequence can be before it is no longer considered "substantially similar." The property of reduced expression is inherent to the mutagenized endogenous nucleotide sequence. It is inherent that the EMS treatment caused a point mutation, as EMS is known to cause point mutations, as taught by Suzuki et al. (page 166).

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ashwin Mehta whose telephone number is 703-306-4540. The examiner can normally be reached on 8:00 A.M to 5:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 703-306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 and 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

January 13, 2003

ASHWIN D. MEHTA, PH.D
PATENT EXAMINER

Notice to Comply	Application No. 09/~~000,000~~ 896,186	Applicant(s) Levin t al.	
	Examiner Mehta	Art Unit 1638	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☒ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other:

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☐ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
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APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
09896,[illegible] 186	06/29/01	LEVIN	PB/5-31481A

EXAMINER	
Mehta	
ART UNIT	**PAPER**
1638	13

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

APPLICANT IS GIVEN 30 days FROM THE DATE OF THIS LETTER WITHIN WHICH TO COMPLY WITH THE SEQUENCE RULES, 37 C.F.R.. §§ 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. § 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for response beyond the six month statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

Any inquiry concerning this communication from the examiner should be directed to Ashwin Mehta, whose telephone number is (703) 306-4540. The examiner can normally be reached on Mondays-Thursdays and alternate Fridays from 8:00AM-5:30PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (703) 306-3218. The fax numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

13 January 2002

ASHWIN D. MEHTA, PH.D
PATENT EXAMINER

Raw Sequence Listing Error Summary

ERROR DETECTED	SUGGESTED CORRECTION	SERIAL NUMBER: 09/896,186

ATTN: NEW RULES CASES: PLEASE DISREGARD ENGLISH "ALPHA" HEADERS, WHICH WERE INSERTED BY PTO SOFTWARE

1	Wrapped Nucleics Wrapped Aminos	The number/text at the end of each line "wrapped" down to the next line. This may occur if your file was retrieved in a word processor after creating it. Please adjust your right margin to .3; this will prevent "wrapping."
2	Invalid Line Length	The rules require that a line not exceed 72 characters in length. This includes white spaces.
3	Misaligned Amino Numbering	The numbering under each 5th amino acid is misaligned. Do not use tab codes between numbers; use space characters, instead.
4	Non-ASCII	The submitted file was not saved in ASCII(DOS) text, as required by the Sequence Rules. Please ensure your subsequent submission is saved in ASCII text.
5	Variable Length	Sequence(s)____contain n's or Xaa's representing more than one residue. Per Sequence Rules, each n or Xaa can only represent a single residue. Please present the maximum number of each residue having variable length and indicate in the <220>-<223> section that some may be missing.
6	PatentIn 2.0 "bug"	A "bug" in PatentIn version 2.0 has caused the <220>-<223> section to be missing from amino acid sequences(s) _____. Normally, PatentIn would automatically generate this section from the previously coded nucleic acid sequence. Please manually copy the relevant <220>-<223> section to the subsequent amino acid sequence. This applies to the mandatory <220>-<223> sections for Artificial or Unknown sequences.
7	Skipped Sequences (OLD RULES)	Sequence(s) _____ missing. If intentional, please insert the following lines for each skipped sequence: (2) INFORMATION FOR SEQ ID NO:X: (insert SEQ ID NO where "X" is shown) (i) SEQUENCE CHARACTERISTICS: (Do not insert any subheadings under this heading) (xi) SEQUENCE DESCRIPTION:SEQ ID NO:X: (insert SEQ ID NO where "X" is shown) This sequence is intentionally skipped Please also adjust the "(ii) NUMBER OF SEQUENCES:" response to include the skipped sequences.
8	Skipped Sequences (NEW RULES)	Sequence(s) _____ missing. If intentional, please insert the following lines for each skipped sequence. <210> sequence id number <400> sequence id number 000
9	Use of n's or Xaa's (NEW RULES)	Use of n's and/or Xaa's have been detected in the Sequence Listing. Per 1.823 of Sequence Rules, use of <220>-<223> is MANDATORY if n's or Xaa's are present. In <220> to <223> section, please explain location of n or Xaa, and which residue n or Xaa represents.
10	Invalid <213> Response	Per 1.823 of Sequence Rules, the only valid <213> responses are: Unknown, Artificial Sequence, or scientific name (Genus/species). <220>-<223> section is required when <213> response is Unknown or is Artificial Sequence
11	Use of <220>	Sequence(s) _____ missing the <220> "Feature" and associated numeric identifiers and responses. Use of <220> to <223> is MANDATORY if <213> "Organism" response is "Artificial Sequence" or "Unknown." Please explain source of genetic material in <220> to <223> section. (See "Federal Register," 06/01/1998, Vol. 63, No. 104, pp. 29631-32) (Sec. 1.823 of Sequence Rules)
12	PatentIn 2.0 "bug"	Please do not use "Copy to Disk" function of PatentIn version 2.0. This causes a corrupted file, resulting in missing mandatory numeric identifiers and responses (as indicated on raw sequence listing). Instead, please use "File Manager" or any other manual means to copy file to floppy disk.

OIPE

RAW SEQUENCE LISTING DATE: 07/19/2001
PATENT APPLICATION: US/09/896,186 TIME: 15:55:45

Input Set : A:\ES.txt
Output Set: N:\CRF3\07192001\I896186.raw

Does Not Comply
Corrected Diskette Needed

3 <110> APPLICANT: Joshua Z. Levin
4 Ken Phillips
5 Greg Budziszewski
6 Fred Meins
7 Zhenya Glazov
9 <120> TITLE OF INVENTION: Methods of Controlling Gene Expression
11 <130> FILE REFERENCE: PB/5-31481A
W--> 12 <140> CURRENT APPLICATION NUMBER:
C--> 13 <141> CURRENT FILING DATE: 2001-06-29
15 <160> NUMBER OF SEQ ID NOS: 34
17 <170> SOFTWARE: PatentIn Ver. 2.1

ERRORED SEQUENCES

see item 10 on Err Summary Sheet (global err)

1503 <210> SEQ ID NO: 34
1504 <211> LENGTH: 24
1505 <212> TYPE: DNA
C--> 1506 <213> ~~ORGANISM:~~ Description of Artificial Sequence:
W--> 1507 Oligonucleotide
W--> 1509 <220> FEATURE:
W--> 1509 <223> OTHER INFORMATION:
1509 <400> SEQUENCE: 34
1510 ttatgagcca ctgacagcat cagg 24
E--> 1514 Pb/5-31481a
E--> 1516 1
E--> 1519 3
E--> 1522 4
E--> 1527 28
E--> 1532 1

delete

Use of n and/or Xaa has been detected in the Sequence Listing. Review the Sequence Listing to insure a corresponding explanation is presented in the <220> to <223> fields of each sequence using n or Xaa.

VERIFICATION SUMMARY DATE: 07/19/2001
PATENT APPLICATION: **US/09/896,186** TIME: 15:55:47

Input Set : **A:\ES.txt**
Output Set: **N:\CRF3\07192001\I896186.raw**

L:12 M:283 W: Missing Blank Line separator, <140> field identifier
L:13 M:271 C: Current Filing Date differs, Replaced Current Filing Date
L:1419 M:220 C: Keyword misspelled or invalid format, <213> ORGANISM for SEQ ID#:25
L:1420 M:259 W: Allowed number of lines exceeded, <213> ORGANISM:
L:1422 M:258 W: Mandatory Feature missing, <220> FEATURE:
L:1422 M:258 W: Mandatory Feature missing, <223> OTHER INFORMATION:
L:1429 M:220 C: Keyword misspelled or invalid format, <213> ORGANISM for SEQ ID#:26
L:1430 M:259 W: Allowed number of lines exceeded, <213> ORGANISM:
L:1432 M:258 W: Mandatory Feature missing, <220> FEATURE:
L:1432 M:258 W: Mandatory Feature missing, <223> OTHER INFORMATION:
L:1439 M:220 C: Keyword misspelled or invalid format, <213> ORGANISM for SEQ ID#:27
L:1440 M:259 W: Allowed number of lines exceeded, <213> ORGANISM:
L:1442 M:258 W: Mandatory Feature missing, <220> FEATURE:
L:1442 M:258 W: Mandatory Feature missing, <223> OTHER INFORMATION:
L:1449 M:220 C: Keyword misspelled or invalid format, <213> ORGANISM for SEQ ID#:28
L:1450 M:259 W: Allowed number of lines exceeded, <213> ORGANISM:
L:1451 M:259 W: Allowed number of lines exceeded, <213> ORGANISM:
L:1453 M:258 W: Mandatory Feature missing, <220> FEATURE:
L:1453 M:258 W: Mandatory Feature missing, <223> OTHER INFORMATION:
L:1454 M:258 W: Mandatory Feature missing, <221> not found for SEQ ID#:28
L:1454 M:258 W: Mandatory Feature missing, <222> not found for SEQ ID#:28
L:1454 M:341 W: (46) "n" or "Xaa" used, for SEQ ID#:28
L:1459 M:220 C: Keyword misspelled or invalid format, <213> ORGANISM for SEQ ID#:29
L:1460 M:259 W: Allowed number of lines exceeded, <213> ORGANISM:
L:1462 M:258 W: Mandatory Feature missing, <220> FEATURE:
L:1462 M:258 W: Mandatory Feature missing, <223> OTHER INFORMATION:
L:1468 M:220 C: Keyword misspelled or invalid format, <213> ORGANISM for SEQ ID#:30
L:1469 M:259 W: Allowed number of lines exceeded, <213> ORGANISM:
L:1471 M:258 W: Mandatory Feature missing, <220> FEATURE:
L:1471 M:258 W: Mandatory Feature missing, <223> OTHER INFORMATION:
L:1477 M:220 C: Keyword misspelled or invalid format, <213> ORGANISM for SEQ ID#:31
L:1478 M:259 W: Allowed number of lines exceeded, <213> ORGANISM:
L:1480 M:258 W: Mandatory Feature missing, <220> FEATURE:
L:1480 M:258 W: Mandatory Feature missing, <223> OTHER INFORMATION:
L:1486 M:220 C: Keyword misspelled or invalid format, <213> ORGANISM for SEQ ID#:32
L:1487 M:259 W: Allowed number of lines exceeded, <213> ORGANISM:
L:1489 M:258 W: Mandatory Feature missing, <220> FEATURE:
L:1489 M:258 W: Mandatory Feature missing, <223> OTHER INFORMATION:
L:1496 M:220 C: Keyword misspelled or invalid format, <213> ORGANISM for SEQ ID#:33
L:1497 M:259 W: Allowed number of lines exceeded, <213> ORGANISM:
L:1499 M:258 W: Mandatory Feature missing, <220> FEATURE:
L:1499 M:258 W: Mandatory Feature missing, <223> OTHER INFORMATION:
L:1506 M:220 C: Keyword misspelled or invalid format, <213> ORGANISM for SEQ ID#:34
L:1507 M:259 W: Allowed number of lines exceeded, <213> ORGANISM:
L:1509 M:258 W: Mandatory Feature missing, <220> FEATURE:
L:1509 M:258 W: Mandatory Feature missing, <223> OTHER INFORMATION:
L:1514 M:254 E: No. of Bases conflict, LENGTH:Input:0 Counted:29 SEQ:34
L:1514 M:320 E: (1) Wrong Nucleic Acid Designator, NUMBER OF INVALID KEYS:9

VERIFICATION SUMMARY DATE: 07/19/2001
PATENT APPLICATION: **US/09/896,186** TIME: 15:55:47

Input Set : **A:\ES.txt**
Output Set: **N:\CRF3\07192001\I896186.raw**

L:1514 M:112 C: (48) String data converted to lower case,
M:254 Repeated in SeqNo=34
L:1532 M:252 E: No. of Seq. differs, <211>LENGTH:Input:24 Found:29 SEQ:34